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RESEARCH**

APPLICATION NUMBER:

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SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date: October 10, 2014

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Director, Division of Pulmonary, Allergy and Rheumatology
Products, CDER, FDA

Subject: Division Director Summary Review

NDA Number: 22-535

Applicant Name: InterMune, Inc.

Date of Submission: May 23, 2014 (original NDA was submitted on November 4, 2009)

PDUFA Goal Date: November 23, 2014

Proprietary Name: Esbriet

Established Name: Pirfenidone

Dosage form: Capsules

Strength: 267 mg capsules

Proposed Indications: Treatment of patients with idiopathic pulmonary fibrosis (IPF)

Action: Approval

1. Introduction

InterMune submitted this 505(b)(1) application for use of pirfenidone 267 mg capsules for the treatment of patients with idiopathic pulmonary fibrosis (IPF). The proposed dose is three capsules (267 mg each) three times a day for a total daily dose of 2403 mg, following a 2 week dose escalation schedule starting with one capsule three times a day for the first week and two capsules three times a day for the second week. Pirfenidone is a new molecular entity of a new class called pyridone, and has been granted orphan drug, fast track, and breakthrough designations. The application is based on clinical efficacy and safety studies. The application was not approved in the first review cycle due to failure of the clinical development program to demonstrate substantial evidence of efficacy. The submitted studies failed to meet their primary efficacy endpoint of change in forced vital capacity in one of two pivotal studies. In the resubmission, the Applicant has provided the results of a new study with pirfenidone in patients with IPF. The new study (Study 016), taken together with the data from the two previously conducted studies (Studies 004 and 006), has resolved the deficiency. This summary review provides an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

IPF is a diffuse progressive parenchymal lung disease of unknown etiology, characterized by fibrotic interstitial infiltrates that are consistent with the histopathologic pattern of

usual interstitial pneumonia.¹ It is the most common type of interstitial lung disease, estimated to affect 132,000 to 200,000 people in the United States. Approximately 50,000 new cases are diagnosed each year, and as many as 40,000 patients in America die from IPF each year. IPF is typically seen in older adults, more commonly in men than women, usually occurring between the ages of 50-70 years, and is characterized by progressive dyspnea, non-productive cough, and progressive pulmonary insufficiency. The natural course of IPF is variable. As the interstitial fibrosis and architectural distortion advance, the lung becomes increasingly non-compliant, and the work of breathing and dyspnea increase. Patients with IPF typically experience slowly progressive worsening of lung function over time, but some experience rapid declines and frequent hospitalizations in the late stage of the disease.² While the course of the disease is variable, the prognosis is uniformly poor, with a median survival of about 3-5 years after diagnosis.

There are no medications approved for the treatment of IPF in the United States. IPF patients are often treated with corticosteroids and immunosuppressive agents, such as azathioprine and cyclophosphamide. No clinical trials have demonstrated a clear clinical benefit for these therapeutic agents and the use of these agents is not FDA-approved. In 2011, the American Thoracic Society issued a statement, citing evidence-based guidelines, that clinical benefit of any drug therapy used in IPF was weak.³ Interestingly, recent trials of historical standard-of-care treatment regimens in IPF have shown increased mortality.⁴ Historically, lung transplantation has been the only therapeutic option for patients with IPF.

Pirfenidone has been studied for various diseases including IPF for a long time. The development of pirfenidone was initiated in the US by Marnac, Inc. InterMune acquired the rights to pirfenidone in the US from Marnac in 2002. Another company called Shionogi, licensed the rights to pirfenidone in Japan. Shionogi received marketing approval for pirfenidone for the treatment of IPF in Japan in October 2008, under the tradename Pirespa as a 200 mg tablet. InterMune was granted marketing authorization for pirfenidone for the treatment of IPF in various countries in Europe starting in 2011 and in Canada in 2012.

¹ ATS/ERS. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am J Respir Crit Care Med*. 2000;161:(2 Pt 1):646-64.

² Martinez FJ, Safrin S, Weycker D, et al. The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med*. 2005;142 (12 Pt 1):963-7.

³ Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. 2011;183:788-824.

⁴ Raghu G, Anstrom KJ, King TE Jr, et al. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med*. 2012 May 24; 366(21):1968-77.

Pertinent regulatory interactions between InterMune and the Agency include an End-of-Phase 2 (EOP2) Meeting in December 2004, and a Pre-NDA meeting in September 2008. At these meetings the Division acknowledged that dose-ranging data were limited and advised inclusion of more than one dose in pivotal efficacy and safety studies. The Division mentioned that a single pivotal study would be unlikely to support approval unless the results were highly persuasive. The Division also raised concerns with the primary endpoint of change in forced vital capacity (FVC). The Division noted that mortality is the ideal primary endpoint for IPF clinical trials and FVC is not an established surrogate for mortality. Further, it is unclear what would constitute a clinically meaningful effect size for FVC. The Division noted that efficacy would be assessed by the totality of the data, including secondary endpoints.

During the first review cycle, the NDA received a Complete Response action (non-approval) due to failure to demonstrate substantial evidence of efficacy. Two studies (004 and 006) were conducted with FVC as the primary endpoint; only one of the studies met the primary endpoint. In order to resolve the deficiencies, the Applicant was asked to conduct another study to demonstrate a statistically significant benefit in all-cause mortality with pirfenidone, or alternatively, demonstrate benefit with FVC as the primary endpoint that replicates the efficacy of pirfenidone compared to placebo, with the all-cause mortality data from the to-be-conducted clinical study pooled with the all-cause mortality data from the two previously conducted studies (004 and 006) providing supportive evidence of benefit. The Applicant conducted another study (016) with FVC as the primary endpoint. The design of Study 016 was discussed at a Type C meeting held in March 2011. The Division raised concern that the duration of Study 016 was 52 weeks, whereas the previously conducted Studies 004 and 006 had been of 72 weeks duration. The earlier failed study 006 showed a statistically positive effect for pirfenidone at 48 weeks that did not persist at 72 weeks. The Division cautioned that shortening the treatment duration to 52 weeks may introduce risk into the clinical development program should a mortality benefit not be demonstrated at this time point, as mortality was being used to justify the use of FVC as the primary efficacy endpoint.

3. Chemistry, Manufacturing, and Controls

The proposed commercial drug product, Esbriet (pirfenidone) capsules, contains 267 mg pirfenidone and standard compendial excipients. The drug product will be packaged in bottles of 270 capsules for a 30-day supply, and in blister trays for a 14-day titration period or a 4-week maintenance period. The active pharmaceutical ingredient will be manufactured at (b) (4). The drug product will be manufactured at (b) (4). The packaging will be performed at (b) (4). All manufacturing and testing facilities associated with this application have acceptable inspection status. The various DMFs associated with the manufacture of the product are adequate. An expiry of 4 years is proposed and supported by submitted data.

4. Nonclinical Pharmacology and Toxicology

InterMune submitted a complete toxicology program that included general toxicology studies of 6 months duration in rats and 9 months duration in dogs, phototoxicity studies in guinea pigs and hairless mice, embryofetal development studies in rats and rabbits, and 2-year carcinogenicity studies in mice and rats. In the general toxicology studies, the target organs of toxicity were liver, thyroid gland, adrenal gland, urinary bladder, and submaxillary glands. The proposed human dose has adequate safety margins for the animal toxicity findings. The phototoxicity studies showed clinical signs of skin phototoxicity with UV radiation. The embryofetal studies showed decreased number of live births and reduced pup viability and body weight. These findings support a pregnancy category C classification for pirfenidone. The mouse carcinogenicity study showed increased incidence of hepatocellular adenomas, carcinomas, and hepatoblastomas. The rat carcinogenicity study also showed increased incidences of hepatocellular adenomas and carcinomas as well as uterine adenocarcinomas and adenomas. These findings do not impact the approval decision given the serious nature of human IPF disease.

5. Clinical Pharmacology and Biopharmaceutics

InterMune submitted a complete and adequate clinical pharmacology program for pirfenidone. Pirfenidone is recommended for administration with food, primarily because the frequency of adverse events (AEs) may be lower with food, compared to fasting. A high fat meal decreases the C_{max} by ~49% and AUC by ~16% compared to fasting. Pirfenidone is primarily metabolized by CYP1A2. The major metabolite, 5-carboxy-pirfenidone is inactive and renally eliminated. There is no significant accumulation of pirfenidone and 5-carboxy-pirfenidone at the proposed dosing regimen. The pharmacokinetics of pirfenidone are affected by co-administration of CYP1A2 inhibitors or inducers. Fluvoxamine (a strong CYP1A2 inhibitor) and ciprofloxacin (a moderate CYP1A2 inhibitor) increased pirfenidone AUC_{0-inf} by 400% and 81% and C_{max} by 70% and 23%, respectively. As a result, the label will recommend decreasing the pirfenidone dose to 1 capsule three times a day (a total of 801 mg daily) when given concomitantly with fluvoxamine and decreasing to 2 capsules three times a day (a total of 1602 mg daily) when given concomitantly with ciprofloxacin. Smoking reduces the systemic exposure (AUC) of pirfenidone by ~54%. Smoking should be avoided when using pirfenidone.

InterMune conducted a thorough QT (TQT) study that did not show an effect on the QT interval; however the study did not demonstrate the effect of the positive control, moxifloxacin, and the supratherapeutic dose (1.6 x therapeutic dose) did not cover the maximum pirfenidone exposure (e.g. 4-fold increase with co-administration of fluvoxamine). However, the clinical program included ECG monitoring and evidence of QT prolongation was not noted. The limitations of the TQT study do not preclude approval.

6. Clinical Microbiology

The microbiological quality of the drug product is controlled by acceptable and suitable testing protocol.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

There was also another study conducted by Shionogi in Japan (Study SP3) for submission to the Japanese regulatory authority. No patient level data were submitted with this application for our review. This review will cover InterMune studies listed in Table 1 and will not further discuss Study SP3.

Table 1. Relevant clinical studies

ID Year*	Study Characteristics † - Patient age - Patient characteristics - Study objective, design - Study duration	Treatment groups ‡	N §	Primary efficacy endpoint ¶	Regions and Countries //
Submitted with the initial NDA					
004 Study 2 [Nov 2008]	- ≥ 40 yr to 80 yr - DLco ≥35% and FVC ≥50% of predicted - Pivotal, R, DB, PC - 72 weeks	Pir 2403 mg/day Pir 1197 mg/day Placebo	174 87 174	Change in percent predicted FVC from baseline to week 72	US, Canada, Mexico, UK, France, Italy, Poland, Australia
006 Study 3 [Nov 2008]	- ≥ 40 yr to 80 yr - DLco ≥35% and FVC ≥50% of predicted - Pivotal, R, DB, PC - 72 weeks	Pir 2403 mg/day Placebo	171 173	Change in percent predicted FVC from baseline to week 72	US, Belgium, Germany, Ireland, Spain, Switzerland, Australia
Submitted with this NDA resubmission					
016 Study 1 [Feb 2014]	- ≥ 40 yr to 80 yr - DLco 30% and FVC ≥50% & ≤90% predicted - Pivotal, R, DB, PC - 52 weeks	Pir 2403 mg/day Placebo	278 277	Change in percent predicted FVC from baseline to week 52	US, Mexico, Peru, Brazil, Croatia, Israel, Singapore, Australia, New Zealand
<p>* Study ID shown (top to bottom) as InterMune's study number, as references in the Esibret product label, and [Year study subject enrollment ended]</p> <p>† R=randomized, DB=double blind, PC=placebo controlled</p> <p>‡ Pir = Pirfenidone total daily dose, divided TID. Because of gastrointestinal adverse events, there was a two week titration to the maintenance dose as follows: days 1 to 7 dose was 801 mg/day, days 8-14 dose was 1602 mg/day</p> <p>§ Intent to treat (ITT)</p> <p>¶ Statistical model for study was rank ANCOVA, with a standardized rank change in FVC as the outcome variable and standardized rank baseline FVC as a covariate</p> <p>// Shown as countries</p>					

b. Design and conduct of the studies

Studies 004 and 006 were similar in design and conduct except for the treatment arms as noted in Table 1. Both were randomized, double-blind, placebo-controlled, parallel group in design, conducted in patients with a diagnosis of IPF, using acceptable diagnostic criteria. Concomitant treatments, such as corticosteroids, cytotoxic drugs, immunosuppressive and immunomodulating agents, and endothelin receptor antagonists were not allowed. Patients who met predefined criteria for acute respiratory decompensation, acute IPF exacerbation, or progression of disease were permitted to receive certain therapies. The primary efficacy variable was the absolute change in percent-predicted FVC from Baseline to Week 72. Secondary efficacy variables included: time to worsening of IPF (defined as time to acute IPF exacerbation, IPF-related death, lung transplantation, or respiratory hospitalization, whichever came first), and progression-free survival (defined as time to first occurrence of either: 10% absolute decline in % predicted FVC, or 15% absolute decline in % predicted DLco, or death). If the primary efficacy analyses from Study 004 and Study 006 each showed efficacy, then the secondary outcome variables were to be analyzed using pooled data from both studies in addition to the individual study analyses. The pooled secondary efficacy analyses were to be considered primary. Safety assessments included recording of adverse events, vital signs, physical examination, clinical laboratory evaluation, and 12-lead ECG.

Study 016 was similar in design to Studies 004 and 006 with an important difference in study duration, 52 weeks versus 72 weeks, and inclusion of patients with lower percent-predicted DLco, higher FEV1/FVC ratio, and longer time since IPF diagnosis. Primary and secondary efficacy variables were similar, and mortality was pre-specified to be examined in a pooled fashion with Studies 004 and 006 as a support for the primary endpoint of FVC. Progression free survival was defined differently compared to previous Studies 004 and 006. In Study 016, a 50 meter decline in 6-minute walk distance replaced the DLco decline criterion for progression-free survival.

c. Efficacy findings and conclusions

The submitted clinical program that included Studies 004 and 006 in the original NDA, and Study 016 submitted in this NDA resubmission supports the efficacy of pirfenidone. Results of the primary efficacy variable are shown in Table 2. The results were statistically significant for Studies 004 and 016.

Table 2. Mean change from baseline in percent predicted FVC to week 72 for studies 004 and 006 and week 52 for study 016 in all randomized patients (rank ANCOVA with imputation*)

	Pirfenidone 2403 mg/day	Pirfenidone 1197 mg/day	Placebo	Difference from Placebo	
				Absolute	p-value
Study 004	-8.0	-9.9	-12.4	4.4	0.01
Study 006	-9.0		-9.6	0.6	0.50
Study 016	-3.7		-6.6	2.9	<0.01

* Imputation of missing data: 0 if patient died; sum of squared mean difference method if patient alive

In the original NDA, among the two studies 004 and 006, the effect size for the positive study (Study 004) was an absolute difference in change from baseline percent-predicted FVC of 4.4%. An evaluation of the change from baseline percent-predicted FVC over time for the two studies is shown in Figure 1. In Study 006, there was a separation of the treatment groups from Week 24 to Week 60, but after week 60, the results for treatment groups were similar. The absolute effect size for FVC that can be considered clinically meaningful and correlate with mortality or other patient-centered outcomes is not known. According to scientific literature and the ATS Consensus Statement⁵, a $\geq 10\%$ increase in FVC over 3 to 6 months can be viewed as a favorable positive response. A continuous responder plot prepared by the Agency's statistical reviewer is shown in Figure 2. The x-axis shows the decline in percent-predicted FVC from baseline (or worsening) at Week 72, and the y-axis shows the corresponding percentage of patients achieving the level of percent-predicted FVC decline or greater. Using an absolute decline in percent-predicted FVC of 10% or greater to define a responder, the results between pirfenidone and placebo groups were similar in Study 006. In Study 004, 20% of patients treated with pirfenidone had at least 10% decline compared to 35% of patients in the placebo group.

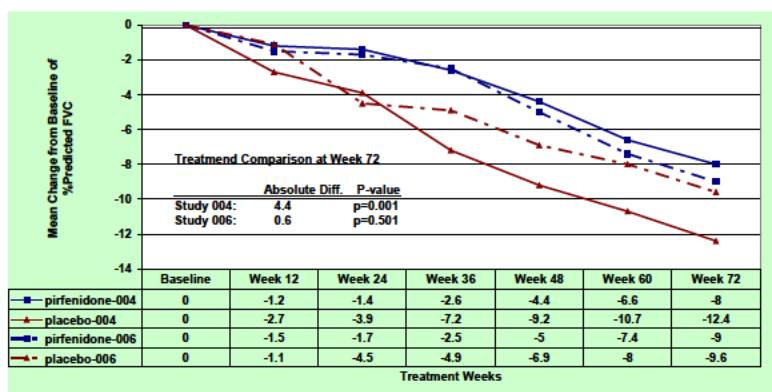


Figure 1. Mean change in percent predicted FVC from baseline, with pre-specified imputation for missing data. Rank ANCOVA.

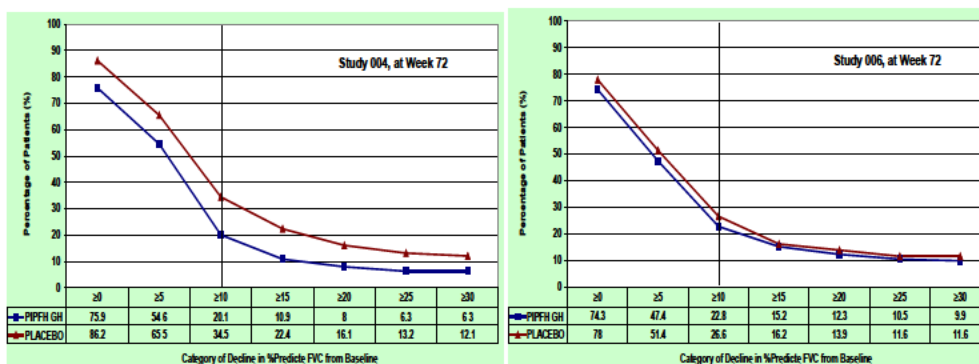


Figure 2. Cumulative % of patients of change from baseline in % predicted FVC.

⁵ American Thoracic Society Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment. Am J Respir Crit Care Med 2000; 161: 646-664.

Study 016 submitted in this NDA resubmission showed that patients receiving pirfenidone had a smaller mean decline in FVC compared to placebo at week 52 (Table 2). The effect size was an absolute difference in change from baseline percent predicted FVC of 2.9%, which was smaller than the previous positive study. A continuous responder plot prepared by the Agency's statistical reviewer is shown in Figure 3. The positive treatment effect of pirfenidone was demonstrated by consistent separation of the curves across the different levels of response. Using an absolute decline in percent-predicted FVC of 10% or greater to define a responder, 17% of patients treated with pirfenidone had a decline of greater than 10% compared to 32% of patients in the placebo group.

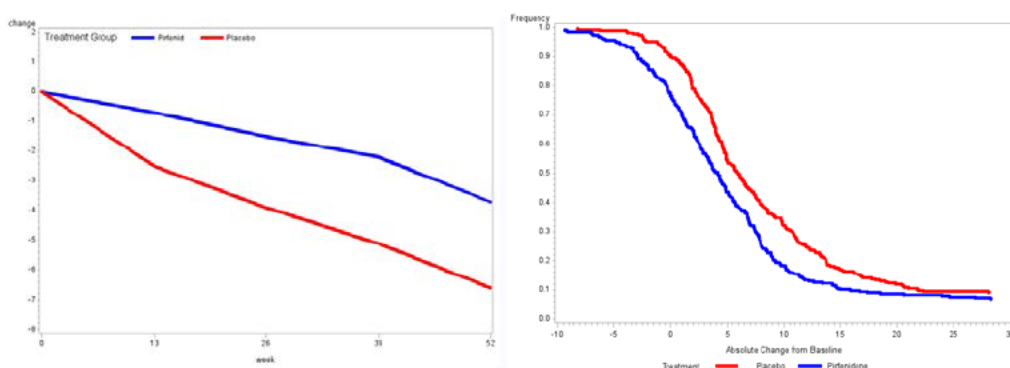


Figure 3. Mean change in percent predicted FVC from baseline (Left Panel), and Cumulative % of patients of change from baseline in % predicted FVC (Right Panel), Study 016

In Study 016, change in 6-minute walk distance was analyzed. The mean decline in 6-minute walk distance was lower in patients treated with pirfenidone compared to placebo (-33.6 vs. -60.2 meters, respectively; difference of 26.7 meters). These results were not robust, as sensitivity analyses did not retain statistically significant results. Further, it is uncertain what magnitude of difference constitutes a clinically meaningful change for a patient with IPF.

Progression free survival, which is a composite of various endpoints as defined in section 7b above, was assessed in all studies. In Study 004, the progression-free survival was statistically significantly different between pirfenidone and placebo, with the result driven primarily by the criterion of decline in FVC. In Study 016, the result of progression-free survival was statistically significantly different between pirfenidone and placebo, with the result driven primarily by the criteria of 6-minute walk distance and decline in FVC. These results are supportive of efficacy, (b) (4)

Mortality is the most relevant endpoint for IPF studies and is the ideal endpoint for assessing efficacy of an IPF therapy. Mortality data were analyzed in various ways by InterMune and by the Agency. Results of Studies 004 and 006 (in the original NDA) and (b) (4)

Study 016 (in this NDA resubmission) are shown in Table 3 and Table 4. Mortality results are shown as vital status (all deaths that occurred during the total study period and defined study follow-up period regardless of whether patients continued study treatment), and as on-treatment (deaths that occurred after the first dose and within 28 days after the last dose). Timing of mortality assessment differed across studies. For Studies 004 and 006 patients enrolled early were treated until the last patient finished 72 weeks of treatment, and mortality was followed until the end of the study (~120 weeks). For Study 016, patients' mortality was followed for 52 weeks. While both the vital status and on-treatment mortality results are important, vital status mortality is generally considered informative of the efficacy of a drug with respect to survival, and on-treatment mortality is generally considered informative of the safety of a drug.

In Studies 004 and 006, the causes of deaths were not adjudicated. Investigators were asked to indicate via a checkbox on the mortality case report form (CRF) whether the deaths were IPF-related. In the analysis of all-cause mortality measured at vital status, mortality benefit was not demonstrated for the two studies individually or pooled. The numerical trend generally favored pirfenidone, but the confidence intervals were large. Statistically significant benefit was seen in the pooled analysis of IPF-related on-treatment mortality. This benefit should be interpreted with caution as it was limited by assessment while on treatment, the post-hoc nature of analysis, and lack of adjudication, which resulted in inconsistent analysis of case narratives when determining the cause of death.

Table 3. Mortality analysis from Studies 004 and 006

	Number of events (%)			Hazard Ratio (95% CI), p-value*
	Pirfenidone 2403 mg/day	Pirfenidone 1197 mg/day	Placebo	
All cause death, vital status at end of study				
Study 004	14 (8.0)	10 (11.5)	20 (11.5)	0.68 (0.34, 1.34), p=0.27
Study 006	18 (10.5)		17 (9.8)	1.06 (0.55, 2.07), p=0.86
Study 004+006	32 (9.3)		37 (10.7)	0.85 (0.53, 1.37), p=0.51
All cause death, on-treatment				
Study 004	11 (6.3)	8 (9.2)	15 (8.6)	0.68 (0.31, 1.49), p=0.34
Study 006	10 (5.9)		15 (8.7)	0.66 (0.30, 1.48), p=0.31
Study 004+006	21 (6.1)		30 (8.7)	0.68 (0.39, 1.18), p=0.17
IPF related death†, vital status at end of study				
Study 004	8 (4.6)	7 (8.0)	15 (8.6)	0.51 (0.22, 1.21), p=0.13
Study 006	14 (8.2)		15 (8.7)	0.94 (0.45, 1.95), p=0.86
Study 004+006	22 (6.4)		30 (8.6)	0.72 (0.42, 1.25), p=0.25
IPF related death†, on-treatment				
Study 004	5 (2.9)	6 (6.9)	11 (6.3)	0.45 (0.16, 1.31), p=0.14
Study 006	7 (4.1)		14 (8.1)	0.49 (0.20, 1.23), p=0.13
Study 004+006	12 (3.5)		25 (7.2)	0.48 (0.24, 0.95), p=0.04
*Hazard ratio based on the Cox proportional hazard model with geographic region (US and ROW) as a factor. P-value based on long-rank test stratified by geographic region (US and ROW)				

In Study 016, the causes of death were adjudicated. Patients who discontinued study treatment before 52 weeks were followed for vital status through 52 weeks and analysis of mortality included events occurring in this extended period. In the analysis of all-cause mortality measured at vital status, a mortality benefit was not demonstrated for Study 016 individually or when pooled with Studies 004 and 006 (Table 4). Patients included in the analysis had pre-specified censoring rules noted in the Table 4 footnote. The numerical trend generally favored pirfenidone. Statistically significant benefit was seen in the pooled analysis truncated at 52 weeks, which was done to make the treatment duration the same for all three studies (Table 4). Such an analysis was pre-specified in the protocol for Study 016, and was intended as a support for the FVC endpoint.

(b) (4)

(b) (4)

Table 4. Mortality analysis from Studies 004, 006, and 016

	Number of events (%)		Hazard Ratio (95% CI), p-value*
	Pirfenidone 2403 mg/day	Placebo	
All cause death, vital status at end of study (72 weeks for 004 and 006[†], 52 weeks for 016)[‡]			
Study 004	11 (6.3)	17 (9.8)	0.61 (0.28, 1.29), p=0.19
Study 006	16 (9.4)	17 (9.8)	0.95 (0.48, 1.87), p=0.87
Study 016	11 (4.0)	20 (7.2)	0.55 (0.26, 1.15), p=0.11
Study 004+006+016	38 (6.1)	54 (8.7)	0.69 (0.46, 1.05), p=0.08
All cause death, vital status at end of study (72 weeks for 004 and 006[†], 52 weeks for 016)[§]			
Study 004	14 (8.0)	20 (11.5)	0.65 (0.33, 1.29), p=0.22
Study 006	18 (10.5)	17 (9.8)	1.07 (0.55, 2.08), p=0.83
Study 016	12 (4.3)	21 (7.6)	0.57 (0.28, 1.16), p=0.11
Study 004+006+016	44 (7.1)	58 (9.3)	0.75 (0.50, 1.11), p=0.14
All cause death, 52 weeks for all studies			
Study 004	5 (2.9)	13 (7.5)	0.37 (0.13, 1.04), p=0.05
Study 006	6 (3.5)	9 (5.2)	0.66 (0.24, 1.87), p=0.44
Study 016	11 (4.0)	20 (7.2)	0.55 (0.26, 1.15), p=0.11
Study 004+006+016	22 (3.5)	42 (6.7)	0.52 (0.31, 0.87), p=0.01
* Hazard ratio based on the Cox proportional hazard model with geographic region (US and ROW) as a factor. P-value based on long-rank test stratified by geographic region (US and ROW)			
[†] Patients enrolled early were treated beyond 72 weeks till last patient finished 72 weeks treatment and mortality was followed toward the end of the study			
[‡] The analysis conducted by InterMune had the following pre-specified censoring rules: the censoring date was defined as the earliest of the last available contact date, or time of lung transplantation (if that occurred), or the end of the treatment period.			
[§] The analysis conducted by FDA statistical team only censored patients that were alive at the end of the follow-up period (120 weeks for Studies 004 and 006, 52 weeks for Study 016)			

The results of the clinical program show consistent positive benefit of pirfenidone in the treatment of IPF. Statistically significant differences in FVC were seen in Studies 004 and 016. Benefit in FVC was supported by mortality where a numerical trend in favor of pirfenidone was noted. There was also benefit noted in other secondary measures such as progression-free survival and 6-minute walk distance.

8. Safety

a. Safety database

The safety assessment of pirfenidone was primarily based on the studies shown in Table

1. The total number of patients exposed to pirfenidone is reasonable to assess safety.

b. Safety findings and conclusion

The submitted data support the safety of pirfenidone for the treatment of IPF. The major safety findings of note in the program were liver injury, gastrointestinal adverse reactions, rash, and photosensitivity.

Deaths, SAEs, and Discontinuations due to AEs:

Deaths are discussed in detail in the efficacy discussion in 7c above. Generally, fewer patients in the pirfenidone group than in the placebo group died within 28 days of the last dose from any cause (28 [4.5%] vs 44 [7.1%], respectively. In both groups, IPF was the most common cause of death [pirfenidone n = 10 (1.6%) vs. placebo n = 21 (3.4%)]. Other common causes of death (death in at least 2 patients) were respiratory failure (5 patients, 0.8% in both groups) and pneumonia (3 patients, 0.5% in both groups).

Non-fatal serious adverse events (SAEs) and discontinuations and drop out from adverse events (AEs) were balanced between pirfenidone and placebo treatment groups. The proportions of patients who experienced at least one SAE were 27% vs. 29% for pirfenidone and placebo groups, respectively. The proportion of patients with an SAE is not surprising given the long duration of the studies and the older population with a severe disease and multiple co-morbidities. The three most frequently reported SAEs (IPF, pneumonia, and respiratory failure) were reported in a smaller proportion of pirfenidone-treated patients compared with placebo-treated patients. SAEs that were reported more frequently in the pirfenidone 2403 mg/day group compared to placebo included the following: coronary artery disease [(n=7 (1.1%) vs. n=3 (0.5%)] and angina pectoris [(n= 6 (1.0%) and n=2 (0.3%)].

Common adverse events (AEs) were reported by almost all patients in the studies, which is not surprising given the long duration of the studies and the characteristic of the patient population (older with IPF). Common adverse events that occurred in $\geq 10\%$ and more frequently in pirfenidone versus placebo-treated patient, in order of decreasing frequency, were: nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastro-esophageal reflux, sinusitis, insomnia, decreased weight, and arthralgia.

AEs of interest:

The Applicant identified a set of AEs of interest based on animal toxicology studies and the observed events in the clinical studies 004, 006, and 016. The AEs that were identified as events of interest were liver-related adverse events, gastrointestinal adverse events, rash and photosensitivity, dizziness and falls, and carcinogenicity.

Liver-related adverse events:

Hepatic events that were SAEs were reported in 6 pirfenidone treated patients (1.0%) and 1 (0.2%) placebo-treated patient. The SAEs in the pirfenidone patients were hepatitis (n=2, 0.3%), abnormal liver function tests (n=2, 0.3%), ALT/AST increase (n=1, 0.2%), and hepatic neoplasm (n=1, 0.2%). None of the SAEs resulted in death. In most of these cases, pirfenidone was permanently discontinued (even when confounding factors were noted), and liver enzyme abnormalities resolved. It is notable that in one patient with a reported SAE of moderate liver function test abnormality, treatment was interrupted, ALT and AST elevations resolved, treatment was restarted, and subsequent liver transaminases were within the normal range or mildly elevated throughout the remainder of study participation.

A Hy's Law case was potentially identified in one patient in one of the three controlled studies. The patient was counted as an SAE of hepatitis. The patient was a 75 year-old male with IPF, diabetes, hypercholesterolemia who was concomitantly taking multiple medications including atorvastatin, naproxen, and metformin. At baseline the patient had normal liver transaminases and total bilirubin elevated to about 1.5 time the upper limit of normal. During the course of treatment his liver transaminases and bilirubin increased (ALT to 5x ULN, AST to 4x ULN, total bilirubin 2.5x ULN), however his alkaline phosphatase was also noted to be elevated (3x ULN). The patient later underwent genetic testing that confirmed the diagnosis of Gilbert's disease and pirfenidone was not re-started. Liver enzyme abnormalities resolved, and the patient later expired due to his underlying IPF.

Two additional cases meeting Hy's Law criteria were identified by the Applicant in the post-marketing database. Both occurred early in treatment (by Week 13), and showed reversal of the elevated liver enzymes on study drug discontinuation.

Liver enzymes were frequently monitored in all three studies. The study protocols allowed for dose reductions or interruptions for ALT or AST elevations 3 to 5x ULN (in the absence of symptoms or bilirubin > 2 x ULN), with subsequent re-titration to full dose, as tolerated. Fifteen pirfenidone-treated patients had a maximum post-baseline ALT or AST elevation of 3 to 5x ULN. Of note, 12 of these patients remained on pirfenidone until study completion, with 7 on a full dose, and 5 on a reduced dose. In the overall safety database, ALT and AST elevations were infrequent, but occurred in a larger proportion of patients on pirfenidone than on placebo. For example, AST elevations 3-5 times of normal were reported in 1.3% and 0.5% in pirfenidone and placebo treated patients, respectively; and ALT elevations 3-5 times of normal were reported in 1.9% and 0.3% in pirfenidone and placebo treated patients, respectively. Elevation of AST or ALT along with elevation of bilirubin was reported in one patient who had Gilbert's disease as described above.

The Applicant proposes in labeling that ALT, AST, and bilirubin should be measured prior to initiation of therapy with pirfenidone in all patients, then monthly for the first 6

months and every 3 months thereafter, and proposed dose adjustments based on results. The Division obtained consultation from the OSE regarding the liver safety signal, in order to better inform the labeling of pirfenidone, as it was unclear if routine monitoring should be included in the labeling. After consultation with our OSE colleagues, the Division has decided that the monitoring and dosage modification guidelines as proposed by the Applicant are reasonable, as they are based on what was done during the clinical development program.

Gastrointestinal adverse events:

The most common GI adverse events reported more frequently in pirfenidone patients when compared with placebo included nausea (36% vs. 16%), diarrhea (26% vs. 20%), dyspepsia (19% vs. 7%), vomiting (13% vs. 6.3%), and GERD (11% vs. 7%). Overall, the GI events tended to be mild to moderate in severity, with few discontinuations ($\leq 1\%$) and few hospitalizations (n=5) overall.

Rash and photosensitivity:

Rash was reported for 30% of pirfenidone patients and 10% of placebo patients. Photosensitivity reactions were reported for 9% of pirfenidone patients versus 1% of placebo patients. The majority of patients who reported rash or photosensitivity reaction did so within the initial 6 months of treatment. There were no rash or photosensitivity events that were considered life-threatening, led to hospitalization, or resulted in death. There were no cases of Stevens-Johnson syndrome, erythema multiforme, pemphigus, or toxic epidermal necrolysis reported.

Dizziness and falls:

Dizziness was reported for more patients in the pirfenidone group as compared with placebo patients (18% vs. 11%, respectively). An analysis of the relationship between falls and dizziness revealed that 6 of 112 (5.4%) pirfenidone patients who reported dizziness fell at some time after the dizziness was reported.

Carcinogenicity:

The animal carcinogenicity study was positive for pirfenidone. The number of cancers in the study was balanced across treatment groups, but the studies were too small to exclude a definitive cancer risk.

c. REMS/RiskMAP

No post-marketing risk evaluation and mitigation strategies are recommended.

9. Advisory Committee Meeting

A Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting was held on March 9, 2010, where the original NDA (that included results from Studies 004 and 006)

was discussed. Questions were asked about the efficacy, safety, and approvability of pirfenidone. The committee was split regarding whether there was substantial evidence of efficacy (7 yes, 5 no). Safety was not a major concern as the committee voted that the safety data were adequate for patients with IPF (9 yes, 3 no). Regarding the approval question, the results were in favor of approval (9 yes, 3 no). Two committee members who voted that there was not sufficient efficacy data voted for approval of pirfenidone. The open public session of the meeting had many patients making emotionally moving statements on the lack of availability of treatment options. After the Advisory Committee meeting, the Agency received many letters and statements from academic physicians with expertise in IPF treatment stating that in their view efficacy was not demonstrated with one of the two studies showing benefit in FVC, and with a small effect size. There were also some letters from patients and patient advocacy groups raising the same concern.

The original NDA was also discussed at a Center Regulatory Briefing on April 16, 2010. The general consensus at the meeting was that efficacy was not demonstrated.

The NDA resubmission (that included results from Study 016) was not discussed at another PADAC meeting. With results of three studies, the efficacy benefit uncertainty is resolved with two studies showing benefit in FVC, benefit in FVC supported by numerical trend in favor of mortality, and other secondary efficacy measures. Safety findings have not changed with results of Study 016 and post-marketing data from other countries.

10. Pediatric

Specific pediatric studies are not necessary because IPF is a disease of adults and does not occur in the pediatric population. Furthermore, as an orphan drug program, pediatric studies are not required.

11. Other Relevant Regulatory Issues

a. DSI Audits

A DSI audit was requested during review of the original NDA for 3 clinical sites based upon high enrollment and favorable outcome for pirfenidone. Final report of the DSI inspections revealed adherence to Good Clinical Practices. Minor deficiencies were noted, but these were isolated and deemed unlikely to impact data integrity and patient safety. During review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. There are no issues with financial disclosures in the studies.

c. Others

There are no outstanding issues with consults received from OPDP, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

There are no issues with the proposed proprietary name Esbriet. The proposed proprietary name was accepted by the DMEPA.

b. Physician Labeling

The applicant submitted a label in the Physician's Labeling Rule format. The labeling was reviewed by various disciplines of this Division, the DMPP, DRISK, DMEPA, SEALD, and OPDP. Various changes to different sections of the label submitted by the Applicant was made to reflect the data accurately and to better communicate the findings to the healthcare providers. The Division and the Applicant have a final agreed upon label.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

Pirfenidone will have patient labeling. There will not be a Medication Guide for pirfenidone.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The Applicant has submitted adequate efficacy data to support approval of pirfenidone for the treatment of IPF. The recommended action for this application is Approval.

b. Risk Benefit Assessment

The overall risk benefit assessment supports approval of pirfenidone for the treatment of IPF. Efficacy data show consistent positive benefit of pirfenidone in the treatment of IPF. Statistically significant improvement of FVC was seen in Studies 004 and 016. Benefit in FVC was supported by a numerical trend in favor of mortality for pirfenidone compared to placebo. There was also benefit noted in other secondary measures such as progression-free survival, and 6-minute walk distance. Safety data analysis show liver-related adverse events, gastrointestinal adverse events, rash, and photosensitivity. For the most part, these appear to be patient tolerability issue, which can be managed by dose adjustment. Liver-related adverse events can occur in a small number of patients, which is outweighed by the benefit provided by pirfenidone in IPF. Demonstration of efficacy for IPF, which is uniformly progressive and fatal, and for which there are currently no approved or effective therapies, firmly establishes a risk-benefit assessment in favor of approval of pirfenidone.

c. Post-marketing Risk Management Activities
None.

d. Post-marketing Study Commitments
None.

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/s/

BADRUL A CHOWDHURY
10/10/2014